## REMARKS

Reexamination and reconsideration in light of the foregoing proposed amendments to the claims and the following remarks is respectfully requested.

Claims 1, 21, 23, 24, 26, 30-32 and 34-49 are pending in this application. Claims 2-20, 22, 25, 27-29 and 33 have been previously canceled. It is proposed to amend claims 1, 21, 23, 24, 26, 35-45 and 47-49, and to cancel claims 30 and 32 by the proposed amendment. No new claims are proposed to be added. The proposed amendments do not added new matter or require a new consideration and/or search. Accordingly, it is respectfully requested that the proposed amendments to the claims be entered to allow the claims. If the Examiner deems the amendment not sufficient to overcome the rejections, then it is requested that the amendment be entered to at least place the application in better condition for appeal.

Applicants note the Examiner's acceptance of the drawing corrections to Figs. 1, 2 and 9. The Examiner noted that Applicants' last response did not address the objections to the drawings with respect to Figs. 3-8, 10 and 11. A copy of the Notice of Draftperson's Patent Drawing Review, as received by the undersigned, is attached to this response as Exhibit A. The top section pertaining to the aforementioned drawing figures was crossed out by someone in the USPTO and specific comments were entered in the comments section with respect to Figs. 1 and 9. Since the top section was crossed out, it was believed that objection raised in the top section of the Notice were entered in error and that Applicants only needed to comply with the objections set forth in the comments section of the form. Clarification is requested.

**Rejection Under 35 U.S.C. § 101**

Claims 1 and 34-43 stand rejected under 35 U.S.C. § 101. According to the Examiner, "the claimed invention is directed to non-statutory subject matter." The Examiner states that "[t]o the degree that the method of claims 1 and 47 are directed to a completely *in silico* method where the obtaining and testing steps are computational in nature rather than laboratory chemistry ..., the claims are considered to be non-statutory as they merely manipulate data." Applicants respectfully disagree.

Claim 1 is not a "completely *in silico* method." The claimed method recites step (C) which requires testing the compound for its ability to either modulate binding of a natural ligand to the insulin receptor (IR), IGF-1 receptor (IGF-1R) or insulin receptor related receptor (IRR), or to modulate signal transduction by binding to IR, IGF-1R or IRR. In order to emphasize this step, it is proposed to amend claim 1 to add step (D) to select a compound tested in step (C) that has the abilities required in step (C). Also, to further emphasize the testing environment, it is proposed to amend step (C) of claim 1 to specify that the compound is tested *in vivo* or *in vitro*. Support for the amendments can be found at page 8, lines 3-8, 19-22 and page 9, lines 3-8 of the specification.

It is not clear from the Examiner's remarks whether claim 47 was intended to be included in this rejection. Assuming, arguendo, that claim 47 is also rejected under 35 U.S.C. § 101, the arguments above for the patentability of claim 1 are applied to claim 47; e.g., compounds that meet the criteria of steps A and B are selected in step C upon experimental determination of the desired $K_d$ or $K_I$.

For the foregoing reasons it is respectfully requested that the rejection of claims 1 and 34-43 under 35 U.S.C. § 101 be reconsidered and withdrawn.

**Rejections Under 35 U.S.C. § 112, First Paragraph**

Claims 1, 21, 23, 24, 26, 30-32 and 34-49 stand rejected under 35 U.S.C. § 112, first paragraph. It is proposed to cancel claims 30 and 32, thereby rendering the rejection as to these claims moot. According to the Examiner, the claims fail "to comply with the written description" requirement on the following grounds.

The Examiner finds that there is no basis in the specification for the phrase "modulates binding of a natural ligand" in claim 1 and to require testing of the compound being tested for its ability to modulate the binding. Applicants respectfully traverse this rejection. With regard to the phrase "modulates binding of a natural ligand," the phrase is supported at page 7, lines 20-23 of the specification when read in conjunction with the description at page 7, lines 16-18 and page 17, lines 19-23 of the specification. Specifically, these sections of the specification when read together provide for the stereochemical interaction between the compound and the receptor site which is adapted to prevent the binding of a natural ligand of the receptor molecule , i.e., to increase or decrease the activity mediated by the receptor molecule. According to the Examiner, "[w]hile page 7 discloses preventing the binding of the natural ligand, the specification does not appear to contemplate or disclose the broader concept of modulation binding of natural ligands." The Examiner has not explained how the disclosure fails to disclose "modulation binding" in such a manner that a person having ordinary skill in the art would not have understood the

meaning of the phrase. The phrase used in the claims and in the specification is "modulates binding," and not "modulation binding." The term "modulate" means "to adjust to or keep in proper measure or proportion" (*Webster's Ninth New Collegiate Dictionary*, Merriam-Webster, p. 763 (1989)). This meaning read in conjunction with the passages cited *supra* in the specification would have led a person having ordinary skill in the art to understand that the stereochemistry of the compound will mediate the activity of the receptor, e.g., to prevent binding of the receptor molecule to the receptor site. An example is explained at page 6, line 35 to page 7, line 12 where the compound interacts with the domains of the receptor molecule. Accordingly, the objected to phrase is supported by the specification of the application and a person having ordinary skill in the art would have understood the broad concept of "modulation binding of natural ligands" from reading the specification as a whole.

The Examiner also finds no written support for the phrase "modulates signal transduction via IR, IGF-1R or IRR" in claim 1 and for testing the compound for its ability to modulate the binding. This claim has been amended to read "...modulates signal transduction by binding to IR, IGF-1R or IRR." Support for this phrase can be found at page 17, lines 19-23 when read in conjunction with the passages at page 17, lines 28-31 and page 6, lines 14-17 of the specification. When these passages are read together, the specification describes that activity of the insulin receptor family is modulated by the compound and that once the compound has been identified as modulating the insulin receptor, the ability of the compound to antagonize signal transduction by binding to a member of the IR family can be assessed. The specification at page

6, lines 14-17 defines the insulin receptor family as including IGF-1R, IR and IRR. Accordingly, the specification supports the phrase objected to by the Examiner.

As for the written description for "testing the compound for its ability to modulate binding," the specification in the paragraph bridging pages 17 and 18 of the specification describes selecting the compound and testing the ability of the compound to antagonize signal transduction using routine cellular assays. Accordingly, the specification provides sufficient written description support for the testing of the compound's ability to modulate binding.

With regard to support for claim 34, support for this claim is provided at page 17, lines 28-31 of the specification. The claim is dependent on claim 1 and requires in step (C)(ii) the testing of the compound for its ability to modulate IR, IGF-1R or IRR mediated cell proliferation. The invention is directed to the insulin receptor family which includes, but is not limited to, IR, IGF-1R or IRR. See page 6, lines 14-17 of the specification. The specification discloses at page 17, lines 28-31, that "[o]nce [the] candidate compounds have been identified, their ability to antagonize signal transduction via the IGF-1R can be assessed using a number of routine *in vitro* cellular assays such as inhibition of IGF-1 mediated cell proliferation." Accordingly, claim 34 is supported by the specification of the present application.

The Examiner has further rejected claims 1, 21, 23, 24, 26, 31, and 34-49 under 35 U.S.C. § 112, first paragraph, as not satisfying the enablement requirement of the statute. In particular, the Examiner finds that the "specification does not exemplify modeling of any compound and a molecule as defined by [claim 1, step (A)(i)-(iii)]" and that the "specification

does not disclose any compounds meeting the structural and functional limitations required by the claims."

The test for enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation. *United States V. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989); *In re Stephens*, 529 F.2d 1343, 1345, 188 USPQ 659, 661 (CCPA 1976). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573, 224 USPQ 409, 411 (Fed. Cir. 1984). It is the function of the specification, not the claims, to set forth the practical limits of operation of an invention. *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977). The Examiner has not established that the claims require undue experimentation for a person having ordinary skill in the art to practice the claimed invention.

Examples exemplifying specific compounds or molecules for step (A)(i)-(iii) of claim 1 are not required to support enablement. The specification, as a whole, must be considered to determine if the invention as disclosed is enabled. The invention is directed to a method of identifying a compound that possesses stereochemical complementarity with the molecule as well as possessing the ability to modulate a molecule of the insulin receptor family. The Examiner has not presented any evidence to show that this concept is not known in the art and

would require undue experimentation by a person skilled in the art to practice the claimed invention in the absence of a recitation of specific compounds.

The Examiner made a finding that "the claims can be considered to be effectively no different from obtaining and testing all potential compounds as all assessed compounds will be obtained and tested." It is proposed to amend claim 1 so that step (B) recites: "selecting and obtaining a compound assessed in step (A) which possesses stereochemical complementarity to the molecule." Not all molecules assessed in step (A) will exhibit stereochemical complementarity to the receptor molecule. Step (B), as it is proposed to be amended, would require a selection from all compounds tested of those exhibiting stereochemical complementarity to the receptor. Those compounds selected in step (B) are then subjected to *in vitro* or *in vivo* testing.

The Examiner also made a finding that the claims do not recite any scoring function or cut-off value to discriminate high ranking compounds from low ranking compounds. It is not necessary to provide these cut-off values, particularly in view of the requirement of a selection being made. The concept of "selecting" relates to a choice being made with respect to the best or most suitable compounds in terms of stereochemical complementarity to the molecule of present interest.

The Examiner made a finding that "the specification does not clearly specify what is required to be performed in assessing 'stereochemical complementarity'". In particular, the Examiner asserts that the specification does not provide a specific definition of "stereochemical complementarity". The Examiner acknowledges that page 6 of the specification discusses

"stereochemical complementarity" in the context of "lock-and-key" visualization, but finds the additional references to "matching intra-site coordinates lining the groove of the particular receptor site" (page 13) and the optimal "fit" (page 14) do not make it clear that the discussions a pages 6, 13 and 14 of these terms are "intended to be embraced by the claims."

The terms "stereochemical complementarity", "matching intra-site surface coordinates" and "optimizing, geometrically or chemically, the fit" are all synonymous terms and are commonly used in the art. The phrase 'stereochemical complementarity' was already well known in the art before the priority date of the present application. For example, a search of the PubMed database using the term "stereochemical complementarity" yielded 31 references. See the list of references attached to this response as Exhibit B. Some examples of these references are set out below:

1. Bransome, E.D. et al.; "Apparent stereochemical complementarity of estrogens and helical cavities between DNA base pairs: implications for the mechanism of action of steroids," *J. Theor. Biol.* 1985 Jan 7; **112**(1):97-108.

2. Hendry, L.B.; "Drug design with a new type of molecular modeling based on stereochemical complementarity to gene structure," *J. Clin. Pharmacol.* 1993 Dec; **33**(12):1173-87.

3. Hendry, L.B and Mahesh V.B.; "Stereochemical complementarity of progesterone, RU486 and cavities between base pairs in partially unwound double stranded DNA assessed by computer modelling and energy calculations, " *J. Steroid Biochem. Mol. Biol.* 1992; **41**:647-651.

Applicants also note that the terms "stereochemical fit" and "shape complementarity" are recited in the claims in U.S. Patent Nos. 4,461,619 and 6,184,241. Copies of the patents are attached as Exhibits C and D, respectively. For example, claim 1 of U.S. Patent No. 4,461,619 defines a method for determining the biological activity of a molecule which includes comparing the stereochemical properties of the molecule with respect to cavities in a nucleic acid complex to determine a "complementary fit", with a fit indicating the biological activity. Further, claim 1 of U.S. Patent No. 6,184,241 defines an aspartic protease/inhibitor complex wherein a portion of the complex has a "shape complementarity" with at least a portion of the substrate binding site of the aspartic protease. A person skilled in the art would have understood that the concepts of "stereochemical fit" and "shape complementarity" are synonymous with "stereochemical complementarity."

The Examiner asserts that the specification does not clearly imply what is required to be performed in assessing stereochemical complementarity. The Applicants submit that this is covered by reference to the docking programs as set forth on pages 14-16 of the specification. These programs take each chemical compound and calculate the strength of its interaction with the selected binding site on the IGF-1R by calculating the H-bonds, the geometric shape complementarity, the hydrophobic interactions, the Van der Waals forces and the salt bridges. All of these parameters contribute to the strength of the interaction. Each compound is placed in a large number of orientations and the calculated strengths of these parameters are recorded for each orientation. A person of ordinary skill in the art would clearly understand what is required

to be performed in assessing stereochemical complementarity in light of the references provided in the specification.

The Examiner contends that the claims "do not contain limitations to cavities, binding sites, or energy optimization." The Examiner concludes that, in the absence of such limitations, a person having ordinary skill in the art would not have known "what positive, active steps must be performed to meet these limitations." Applicants respectfully traverse. The Examiner has not explained her basis as to why these alleged limitations must be present in the claims. Further, the Examiner has not presented any evidence or cogent scientific reasoning to support her conclusion.

The Examiner also contends that the claims do not "require finding a binding pocket, using a known binding pocket or using a docking program" and that the claims are not limited accordingly. The Examiner has not explained why or presented any cogent scientific reasoning as to why any of these are necessary limitations that must be included in the claims. The finding of a suitable binding site is inherent in the claim language. For example, a person skilled in the art would understand that the phrase "assessing the stereochemical complementarity between the compound and a molecule" requires a comparison between the size and shape of a binding pocket within the molecule and a putative ligand. The Examiner's attention is directed to the Ring et al. (1993) paper which was submitted as Exhibit C with the last response. The paper describes using the Dock program to select ligands "with the best shape-complementarity scores" when compared to a three-dimensional models of proteases.

The claims require assessing the complementarity between the compound and the receptor molecule. The original claim language referred to assessing the stereochemical complementarity between the compound and a "topographic region" of the molecule. It is Applicants' position that the "topographic region" referred to a potential binding site on the receptor molecule. At the interview with the Examiner last year on June 24, 2003, the Examiner suggested simply removing the term "topographic region" on the ground that the phrase "assessing the stereochemical complementarity between the compound and molecule" was clearer. We adopted the Examiner's suggestion and amended the claim accordingly.

The Examiner also rejects claims 21, 23-24 and 26 which are directed to computer-assisted methods for identifying potential compounds. The Examiner states that the specification provides no guidance on what a criteria data set must include or how it is generated. The Examiner also contends that the specification does not identify any database that could be used in the method as claimed. The way in which the criteria data set is generated is clear from the claim language. In particular, it would be clear to a person having ordinary skill in the art that the criteria data set generated represents a three-dimensional structure that has stereochemical complementarity with the IGF-1R molecule. This criteria data set is then compared with chemical structures stored in a database. As explained in the specification at page 15, lines 3 - 9, databases such as the Cambridge Structural Database System or the Protein Data Bank can be searched for molecules which approximate the shape defined by the "criteria data set".

For all of the foregoing reasons, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claim 1, 21, 23, 24, 26, 31 and 34-49 under 35 U.S.C. § 112, first paragraph.

**Rejection Under 35 U.S.C. § 112, Second Paragraph**

Claims 1, 21, 23, 24, 26, 30-32 and 34-49 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. It is proposed to cancel claims 30 and 32 has been canceled, thereby rendering the rejection as to these claims moot.

The Examiner made a finding that claim 1 is unclear with respect to the phrases "natural ligand" and "signal transduction via IR, IGF-1R or IRR." Applicants respectfully traverse. The phrases would have been clearly understood by a person having ordinary skill in the art reading the specification. In particular, the term 'natural ligand' is well known in the art. Attached as Exhibit E is a summary from the USPTO web site of granted US patents where the term "natural ligand" occurs in the abstracts or claims. The term does not relate to the setting, i.e. *in vivo* or *in vitro*, but rather to the ligand which binds to a receptor and which exists in nature, i.e. it is not artificial. The term does not exclude synthesized organic compounds, if those compounds in fact exist in nature and are ligands of the IR, IGF-1R or IRR. It is proposed to amend claim 1 to make it clear that signal transduction is modulated by binding to IR, IGF-1R or IRR.

The Examiner finds that the phrases "substantially as shown" and "form an equivalent three-dimensional structure" to be indefinite and unclear. In order to obviate the rejection, it is proposed to delete the term "substantially" from the claims. As for the objection to the phrase "form an equivalent 3-dimensional structure," this phrase would have been clearly understood by

a person skilled in the art from reading the specification. It is important to note the context in which this phrase is used in the specification. The context is as follows:

> amino acids present in the amino acid sequence of IR or IRR, that form an equivalent three-dimensional structure to that of the molecule as depicted in Figure 1....

A person having ordinary skill in the art would have been well aware that members of the insulin receptor family (i.e. IR, IGF-1R and IRR) share equivalent structural domains, such as the L1, L2, and Cys-rich domains. It would have been clear then to such a person, that the phrase "form equivalent three-dimensional structure" in the claims refers to a set of amino acids in IR and IRR that form the equivalent domains to those formed by amino acids 1-462 of IGF-1R.

The Examiner finds that the phrase "which are structurally similar to a portion of said criteria data set" in claim 21 is unclear because "[i]t is unknown how much of the criteria data set constitutes 'a portion'." It is proposed to amend the phrase in claim 21 to delete the objected to term "a portion" so that the phrase as amended reads: "which are structurally similar to said criteria data set." It is believed that by this proposed amendment, the rejection would be overcome.

The Examiner rejected claims 23 and 24 on the basis that the phrase "selected in steps (d) and (e)" is unclear. In order to obviate this rejection, it is proposed to amend the phrase to read: "selected in step (d) or outputted in step (e)." It is believed that by this amendment that the objection to the phrase is overcome.

Claims 35, 37 and 38 have been rejected on the basis that there is no antecedent basis for "or more subsets". The objected to language appears in claims 35 and 37, but not in claim 38.

Accordingly, it is requested that the rejection as to claim 38 be reconsidered and withdrawn. As to claims 35 and 37, it is proposed to amend these claims to change the phrase "one or more subsets" to --subset--. It is believed that by this amendment, the rejection is overcome.

The Examiner finds that claims 39 and 40 are "confusing in adding the step of modifying the compound" because the claims do "not make clear if this is performed before or after obtaining in step (B) or before or after testing in step (C)." It is proposed to add the phrase "selected in step (B) or step (D)" to obviate the rejection by the Examiner.

Finally, the Examiner has objected to claim 47 as being unclear because it is not clear whether the $K_d$ or $K_I$ is "a predicted, calculated or experimentally determined value." It is proposed to amend claim 47 to specify that the $K_d$ and $K_I$ are "experimentally determined." Also, it is proposed to amend claims 47 and 48 to correct an obvious error to change $K_b$ to $K_d$.

For all of the foregoing reasons, it is respectfully requested that the rejection of claims 1, 21, 23, 24, 26, 31 and 34-49 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

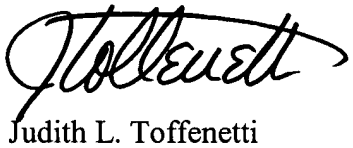
**CONCLUSION**

It is submitted that the claims 1, 21, 23, 24, 26, 31 and 34-49 are in compliance with the provisions of 35 U.S.C. § 101, and the first and second paragraphs of 35 U.S.C. § 112. Accordingly, favorable reconsideration of the claims is requested in light of the preceding proposed amendments and remarks. It is requested that the proposed amendments be entered. Allowance of the claims is courteously solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT, WILL & EMERY



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Form PTO 948 (Rev. 03/02) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 9/555,275

# NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 8-30-01 are:

A. ☑ approved by the Draftsperson under 37 CFR 1.84 or 1.152.

B. ☑ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be sumitted according to the instructions on the back of this notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   - ___ Color drawings are not acceptable until petiton is granted. Fig(s) _____
   - ___ Pencil and non black ink not permitted. Fig(s) _____
2. PHOTOGRAPHS. 37 CFR 1.84(b)
   - ___ 1 full-tone set is required. Fig(s) _____
   - ___ Photographs may not be mounted. 37 CFR 1.84(e).
   - ___ Poor quality (half-tone). Fig(s) _____
3. TYPE OF PAPER. 37 CFR 1.84(e)
   - ___ Paper not flexible, strong, white, and durable. Fig(s) _____
   - ___ Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted. Fig(s) _____
   - ___ Mylar, velum paper is not acceptable (too thin). Fig(s) _____
4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:
   - ___ 21.0 cm by 29.7 cm (DIN size A4)
   - ___ 21.6 cm by 27.9 cm (8 1/2 x 11 inches)
   - ___ All drawing sheets not the same size. Sheet(s) _____
   - ___ Drawings sheets not an acceptable size. Fig(s) _____
5. MARGINS. 37 CFR 1.84(g): Acceptable margins:

   Top 2.5 cm Left 2.5cm Right 1.5 cm Bottom 1.0 cm SIZE: A4 Size

   Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: 8 1/2 x 11

   Margins not acceptable. Fig(s) _____
   - _____ Top (T) _____ Left (L)
   - _____ Right (R) _____ Bottom (B)
6. VIEWS. 37 CFR 1.84(h)

   REMINDER: Specification may require revision to correspond to drawing changes.

   Partial views. 37 CFR 1.84(h)(2)
   - ___ Brackets needed to show figure as one entity. Fig(s) _____
   - ☑ Views not labeled separately or properly. Fig(s) 1, 9
   - ___ Enlarged view not labeled separetely or properly. Fig(s) _____
7. SECTIONAL VIEWS. 37 CFR 1.84 (h)(3)
   - ___ Hatching not indicated for sectional portions of an object. Fig(s) _____
   - ___ Sectional designation should be noted with Arabic or Roman numbers. Fig(s) _____
8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   - ___ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) _____
9. SCALE. 37 CFR 1.84(k)
   - ___ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction: Fig(s) _____
10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
    - ☑ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality). Fig(s) 3-8, 10, 11
11. SHADING. 37 CFR 1.84(m)
    - ___ Solid black areas pale. Fig(s) _____
    - ___ Solid black shading not permitted. Fig(s) _____
    - ___ Shade lines, pale, rough and blurred. Fig(s) _____
12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
    - ☑ Numbers and reference characters not plain and legible. Fig(s) 1-11
    - ☑ Figure legends are poor. Fig(s) 1-11
    - ___ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) Fig(s) _____
    - ___ English alphabet not used. 37 CFR 1.84(p)(2) Figs _____
    - ___ Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3) Fig(s) _____
13. LEAD LINES. 37 CFR 1.84(q)
    - ___ Lead lines cross each other. Fig(s) _____
    - ___ Lead lines missing. Fig(s) _____
14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
    - ___ Sheets not numbered consecutively, and in Arabic numerals beginning with number 1. Sheet(s) _____
15. NUMBERING OF VIEWS. 37 CFR 1.84(u)
    - ___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) _____
16. CORRECTIONS. 37 CFR 1.84(w)
    - ___ Corrections not made from prior PTO-948 dated _____
17. DESIGN DRAWINGS. 37 CFR 1.152
    - ___ Surface shading shown not appropriate. Fig(s) _____
    - ___ Solid black shading not used for color contrast. Fig(s) _____

COMMENTS FIG. 1 SHOULD BE LABELED AS FIG. 1, FIG. 1A-1, 1A-2 1A-3 AND SO-ON UNTIL ALL OF FIGURE 1 HAS BEEN LABELED.

FIG. 9 SHOULD BE LABELED AS FIG. 9A, 9B

REVIEWER J. CHISF DATE 11-5-02 TELEPHONE NO. 703 305 8430

ATTACHMENT TO PAPER NO. 20

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**ABST/"natural ligand" OR ACLM/"natural ligand"**: 26 patents.
*Hits 1 through 26 out of 26*

ABST/"natural ligand" OR ACLM/"natural ligand"

| | PAT. NO. | Title |
|---|---|---|
| 1 | 6,692,964 | Methods for transfecting T cells |
| 2 | 6,638,914 | Pharmaceutical administration of adenosine agonists |
| 3 | 6,566,079 | Methods for analyzing protein binding events |
| 4 | 6,518,480 | Selective target cell activation by expression of a G protein-coupled receptor activated superiorly by synthetic ligand |
| 5 | 6,485,929 | Method for inhibiting CD95-independent apoptosis in AIDS |
| 6 | 6,479,258 | Non-stochastic generation of genetic vaccines |
| 7 | 6,475,733 | Cell surface receptors for the detection and identification of compounds |
| 8 | 6,444,438 | Method for the preparation of a protein by yeasts using an inducible system, vectors and correspondence transformed strains |
| 9 | 6,352,694 | Methods for inducing a population of T cells to proliferate using agents which recognize TCR/CD3 and ligands which stimulate an accessory molecule on the surface of the T cells |
| 10 | 6,310,078 | Substituted amino acids as erythropoietin mimetics |
| 11 | 6,306,595 | Design of drugs involving receptor-ligand-DNA interactions |
| 12 | 6,287,874 | Methods for analyzing protein binding events |
| 13 | 6,262,234 | Nuclear receptor polypeptide ZPPAR4 |
| 14 | 6,258,358 | Targeted immunostimulation with bispecific reagents |
| 15 | 6,248,332 | Targeted immunostimulation with bispecific reagents |
| 16 | 5,925,349 | Treating inflammation via the administration of specific sulfatase enzymes and/or sulfation inhibitor |
| 17 | 5,888,741 | Computer-based design and screening of molecules using DNA interactions |
| 18 | 5,888,738 | Design of drugs involving receptor-ligand-DNA interactions |
| 19 | 5,786,454 | Modified SH2 domains |
| 20 | 5,766,856 | Diagnostic method for evaluating advanced glycosylation endproducts using MAC-2 receptor |
| 21 | 5,705,335 | Design of drugs involving receptor-ligand-DNA interactions |

22 5,695,752 Treating inflammation via the administration of specific sulfatase enzymes and/or sulfation inhibitor
23 5,512,268 Polymeric shells for medical imaging prepared from synthetic polymers, and methods for the use thereof
24 5,506,210 Phosphosugar-based anti-inflammatory and/or immunosuppressive drugs
25 5,434,052 Complementation assay for drug screening
26 5,393,737 Cytotoxic drug conjugates for treatment of neoplastic diseases

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## AMENDMENT

*A listing of the claims presented in this patent application appears below. This listing replaces all prior versions and listing of claims in this patent application.*

**Claim 1 (currently amended):** A method of identifying a compound which modulates binding of a natural ligand to the EGF receptor, ErbB3 or ErbB4, or which modulates signal transduction ~~via~~ by binding to the EGF receptor, ErbB2, ErbB3 or ErbB4, which method comprises the steps of:

(A) assessing the stereochemical complementarity between the compound and ~~the~~ a molecule, wherein the molecule comprises:

(i) amino acids 1-621 of the EGF receptor positioned at atomic coordinates ~~substantially~~ as shown in Figure 6;

(ii) one or more subsets of said amino acids related to the coordinates shown in Figure 6 by whole body translations and/or rotations; or

(iii) amino acids present in the amino acid sequence of ErbB2, ErbB3 or ErbB4, which form an equivalent three-dimensional structure to that of the receptor site defined by amino acids 1-621 of the EGF receptor positioned at atomic coordinates ~~substantially~~ as shown in Figure 6;

(B) ~~obtaining~~ selecting a compound assessed in step (A) which possesses stereochemical complementarity to the molecule; [and]

(C) testing the compound *in vivo* or *in vitro* for its ability to

(i) modulate binding of a natural ligand to the EGF receptor, ErbB3 or ErbB4, or

(ii) modulate signal transduction ~~via~~ by binding to the EGF receptor, ErbB2, ErbB3 or ErbB4[[.]]; and

(D) selecting a compound tested in step (C) that has the ability to

(i) modulate binding of a natural ligand to the EGF receptor, ErbB3 or ErbB4, or

(ii) modulate signal transduction by binding to the EGF receptor, ErbB2, ErbB3 or ErbB4.